REVIEW

Department of Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, USA

Formulation approaches for orally administered poorly soluble drugs

S. PINNAMANENI, N. G. DAS and S. K. DAS

Despite having pharmacodynamic or target activity, many drugs fail in the drug development process due to poor bioavailability, and presently marketed conventional dosage forms of poorly soluble drugs employ high doses leading to potential toxicity. The introduction of the Biopharmaceutic Classification System (BCS) has provided a basis to categorize drugs based on the two major parameters affecting absorption, solubility and permeability. Several techniques can be employed to enhance the absorption and bioavailability of poorly soluble and poorly permeable drugs based on the BCS concept. This article is an attempt to summarize the development of various formulation approaches that are currently employed to enhance bioavailability of orally administered poorly soluble drugs.

Contents

1. Introduction

Solubility is one of the key determinants of the oral bioavailability of a drug. Due to poor aqueous solubility, many drug candidates become unsuccessful to reach the market in spite of exhibiting potential pharmacodynamic activity. Also, poorly aqueous soluble drugs currently on the market are administered at much higher individual doses than actually desired to achieve necessary plasma levels. Consequently, toxicity problems reduce the convenience and patient compliance. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation. This discussion focuses on the formulation approaches to improve aqueous solubility and thus the bioavailability of the poorly soluble drugs.

1.1. Understanding biopharmaceutical principles and the biopharmaceutic classification system (BCS)

Up to forty one percent of the drug candidates fail in the drug development process due to their poor biopharmaceutical properties [1]. An understanding of the concept of BCS gives an insight to deal with various situations and combating bioavailability problems of various orally administered drugs. A drug has to cross several biological membranes before reaching the site of action. For orally administered drugs, the entire process can be described as the LADME system showing that the liberation, absorption, distribution, metabolism and elimination are involved in eliciting a response [2]. Biopharmaceutics is the study of the influence of the physicochemical properties of drugs and products on the drug delivery to the body under normal or pathological conditions [3]. Biopharmaceutical considerations are absolutely important to establish the bioavailability of a drug. The Code of Federal Regulations (CFR 21.320.1), in the US, defines bioavailability as 'the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action'.

Fick's First Law can mathematically represent the absorption process by passive transport,

$$J_w = P_w \times C_w \quad (1)$$

where J_w is the mass transport or drug flux (mass/area/time) through the intestinal wall at any position and time, P_w is the effective permeability of the membrane and C_w is the drug concentration at the intestinal surface [4].

The above equation clearly shows that the permeability and solubility of a drug are the two fundamental parameters affecting the absorption process by passive diffusion. These parameters form the basis for the Biopharmaceutic Drug Classification System (BCS) that classifies all the drugs into four categories as shown in Table 1 [5]. The Class I drugs represent no bioavailability problem and hence are not difficult to formulate for oral administration. The Class IV drugs, because of their poor biopharmaceutical properties, are the most difficult to deliver. These drugs are not preferred for oral administration except in cases where they are potent enough to be effective at low plasma levels. The role of medicinal chemists and pharmaceutical scientists comes into play in the case of Class II and Class III drugs, whose properties can be conveniently modified to enhance the bioavailability when orally administered.

Table 1: BCS classification of drugs [5]

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

1.2. Dimensionless numbers in BCS

The BCS also defines three dimensionless numbers based on physicochemical and physiological parameters to characterize drug substances. These include absorption number (An), dissolution number (Dn) and dose number (Do). In an ideal situation, it would be desirable that a drug possesses high An, high Dn and low Do. High values of An and Dn ensure that the absorption time and dissolution time of the drug are not limited by the its residence time in the gastrointestinal tract while low Do guarantees complete dissolution of the dose administered. A classical example to illustrate the concept of the dimensionless numbers is the case of the Class II drugs, digoxin and griseofulvin. Both drugs have a poor aqueous solubility of approximately 20 μg/ml. However, the normally administered dose of griseofulvin is almost 1000 times higher than that of digoxin. Thus the volume of water required to dissolve a normal dose of griseofulvin is much higher than that required to dissolve digoxin. In terms of BCS, both drugs have low Dn. At the same time, the Do of griseofulvin is much higher compared to that of digoxin. Analyzing the situation, bioavailability of digoxin can be enhanced by increasing its Dn. This can be achieved by decreasing the particle size of the drug, thus increasing its dissolution rate. However, for griseofulvin, complete absorption is possible only when its Do is lowered by enhancing its solubility through the use of formulation excipients. This is true because it is impossible to administer a large enough volume of fluid along with the normal dose of griseofulvin [5–8].

2. Solubility

2.1. Factors affecting solubility

As mentioned before, solubility of a drug is one of the critical biopharmaceutical parameters determining the absorption of the drug in the GI tract. Regardless of the mechanism of drug transport in the GI tract, excepting endocytosis, the drug should be present in soluble form to be absorbed [2]. Poorly soluble drugs have a low Dn, in the sense that their dissolution time is longer than the residence time in the GI tract resulting in poor bioavailability and thus subtherapeutic levels. Drugs with aqueous solubility less than 100 μg/ml generally present bioavailability problems [9]. The critical factors affecting the kinetics of drug dissolution can be identified from the Nerst-Brunner and Levich modifications (incorporating the value of the effective surface area of the solid available for dissolution, A) of the Noyes-Whitney equation as below [10–13]:

$$DR = \frac{dX_d}{dt} = \frac{A \cdot D}{\delta} (C_s - X_d/V) \qquad (2)$$

where DR is the dissolution rate, A is the effective surface area of the solid drug, D is the diffusion coefficient of the drug, δ is the effective diffusion boundary layer thickness adjacent to the dissolving surface, C_s is the saturation solubility of the drug under lumenal conditions, X_d is the amount of drug already in solution and V is the volume of the dissolution medium. Although physicochemical parameters play a role in determining above-mentioned critical factors, physiological conditions are primarily responsible in determining the dissolution rate (Table 2).

2.2. Approaches to improve solubility

Saturation solubility constitutes the concentration gradient and is one of the key factors affecting drug dissolution and consequent absorption. The aqueous solubility of a solid compound is dependent on the intermolecular interactions within the solid, intermolecular interactions in the solution and the entropy changes accompanying fusion and dissolution. The solubility of any solute can be estimated from eq. (3) below:

$$\log X_w = \log X_i - \log \gamma_w \qquad (3)$$

where X_w is the observed mole fraction solubility of any solute, X_i is the ideal mole fraction solubility and γ_w is the activity coefficient in water [2, 14]. The ideal mole fraction solubility is dependent on the nature of the chemical compound while the activity coefficient is dependent on the solute-solvent interactions that are controlled by environmental conditions such as temperature and pressure. Thus, there are two approaches that can be sought for enhancing solubility of drugs. Firstly, the ideal mole fraction solubility of a compound could be increased by bringing about modifications in the chemical structure of the compound, or alternatively, by solid-state manipulations. Secondly, the activity coefficient can be decreased by modifying the formulation of drug [2].

Chemical modifications can be brought about by incorporating polar or ionizable groups or groups that decrease melting point without altering the basic pharmacophore structure of the compound, or by using soluble prodrugs, or salts [2, 15, 16]. Polar group incorporation to enhance solubility led to the development of the anti-HIV drugs, indinavir and ritonavir [2, 17, 18]. The prodrug approach has been employed in case of the ACE inhibitor, enalapril, which is an ester form of the drug enalaprilat. The use of water-soluble salts is the most commonly used approach to enhance bioavailability [19]. A few examples include indinavir sulfate, verapamil hydrochloride, tamoxifen citrate, phenytoin sodium, etc. All of these have improved

Table 2: Physicochemical and physiological parameters important for drug dissolution in the gastrointestinal tract [10]

Factor	Physicochemical parameter	Physiological parameter
Surface area of drug	particle size, wettability	surfactants in gastric juice and bile
Diffusivity of drug	molecular size	viscosity of luminal contents
Boundary layer thickness		motility patterns & flow rate
Solubility	hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile, food components
Amount of drug already dissolved		permeability
Volume of solvent available		secretions, co-administered fluids

aqueous solubility compared to their parent compounds. Even if the free acid or base from the salt finally precipitates due to the pH variations in the GI tract, the increased surface area provided by the smaller particles enhances the dissolution rate [20].

The various formulation approaches to enhance solubility that are presently employed include cosolvency, reducing particle size, modification of the crystal habit, complexation, and solubilization by surfactants and drug dispersion in carriers [21]. In general, formulation approaches are preferred over chemical modification as they are usually less time consuming and less resource intensive. This is where the role of a formulation scientist comes into play.

3. Permeability

It is also important to consider the other key biopharmaceutic parameter, permeability, while formulating a drug for oral administration. A good aqueous solubility of drug substances does not always ensure good absorption. Since biological membranes are amphiphilic in nature, a drug should have an optimum logP or logD value (logarithm of the partition coefficient or logarithm of distribution coefficient respectively) in order to permeate the membrane. The Pfizer Central Research Division, CT, has come up with a pneumonic, "the rule of 5", to predict permeability of compounds based on a set of compounds entering the phase II clinical trials. The rule states that a poor permeation is likely if any of the two parameters are out of range including more than 5 H-bond acceptors, more than 10 H-bond donors, the molecular weight greater than 500 and the Log P (calculated Log P) value greater than 5. However, drugs that are substrates of biological transporters are exceptions to the rule [22]. Thus, either chemical modification of the drug compound or permeation enhancers have to be employed in cases where permeation represents a problem in absorption. Various formulation approaches that are under investigation to enhance permeability include metabolic inhibitors, ion pairing and complexation agents, membrane permeation enhancers including fatty acids, glycerides, bile salts and analogues, chelating agents and salicylates and finally lipid adjuvants [23].

4. Formulation approaches for improving solubility

Solubility enhancement is more appropriate for Class II drugs to prevent an erratic absorption profile. Some of the formulation approaches currently employed to improve aqueous solubility will be discussed in the following sections. The selection of one particular approach for formulation depends on various factors including the nature of the drug and the focus of research of the formulation scientists. It is important to note that more than one formulation approach can be sought for a particular drug compound. The selection of a particular formulation approach rather than another depends on the optimum bioavailability that can be achieved.

4.1. Reduction in particle size

Both micronization and nanosuspension approaches employ reduction of the drug particle size for improving bioavailability. However, each of the techniques employs different equipment to achieve particle size reduction to different extent. Nanosuspension is a more recent strategy and has a better potential when compared to micronization.

4.1.1. Micronization

The major mechanism by which micronized drug particles improve absorption is by increasing the dissolution rate, made possible by the drastic increase in surface area of the drug exposed to the GI fluids. Micronization of drugs is done by milling techniques including jet mill and rotor stator colloid mills that result in a wide particle size range of 0.1–25 μm [24]. This technique has been employed for drugs such as griseofulvin, digoxin, spironolactone, phenytoin, progesterone, diosmin and sulfadiazine [25, 26]. Although applicable to certain drugs, micronization is not suitable for drugs having a high dose number (Do). This is because the technique does not change the saturation solubility of the drug. Moreover, due to the wide particle size distribution, there is crystal growth, or specifically referred to as Ostwald ripening, eventually increasing the particle size [27]. This occurs due to different saturation solubilities and concentration gradients between the boundary layers of smaller particles (<1 μm) and larger particles resulting in supersaturation and subsequent drug crystallization. The process proceeds until the finer particles are completely eliminated [28].

4.1.2. Nanosuspensions

The advantages offered by nanosuspensions are improved bioavailability by increased dissolution rate, increase in saturation solubility, (C_s) of the drug, absence of Ostwald ripening, and mucoadhesive nature. The increased dissolution rate is due to larger surface area exposed while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained eliminating the concentration gradient factor. The increased adhesiveness is due to the fine nature of the drug particles, which can further be enhanced by surface modifications of the nanoparticles [29]. The increase in saturation solubility generally occurs for particles below 1–2 μm in size. The increase in the intrinsic dissolution rate can be explained by Kelvin, Ostwald-Freundlich and Prandtl equations [28, 30, 31]. Applying the Kelvin equation given below to a solid phase, there is increased dissolution pressure with decreasing particle size thus increasing the saturation solubility.

$$\ln \frac{P}{P_0} = \frac{2\gamma V}{rRT} \cos \theta \,, \tag{4}$$

where P is the equilibrium vapor pressure (replace with dissolution pressure) of the liquid in a pore of radius r, P_0 is the equilibrium pressure of the same liquid on a plane surface, γ is the surface tension, V is the molar volume of a liquid, θ is the contact angle with which the liquid meets the pore wall, R is the gas constant and T is the absolute temperature.

The relationship between particle diameters and solubilities can also be explained by the Ostwald-Freundlich equation given below.

$$\log \frac{Cs}{C_\infty} = \frac{2\sigma V}{2.303RT\varrho r} \,, \tag{5}$$

where C_s is the solubility, C_∞ is the solubility of the solid consisting of large particles, σ is the interfacial tension, V is the molar volume of the solid particles, R is the gas constant, T is the absolute temperature, ϱ is the density of the solid and r is the particle radius.

The Prandtl equation below relates the diffusional distance, (h) in the Noyes-Whitney equation for smaller particles with increased concentration gradient.

$$h_H = k \cdot (L/V)^{1/2} \tag{6}$$

where L is the length of the surface in the direction of flow, k is a constant, V is the relative velocity of the flowing liquid against a flat surface and h_H is the hydrodynamic boundary layer thickness.

There are basically three techniques for the production of nanosuspensions including precipitation, pearl milling for NanoCrystals®, and high-pressure homogenization for DissoCubes®. The precipitation method requires drugs soluble in an organic phase, which is miscible with water. When the organic drug solution is added to the aqueous surfactant solution, precipitation of nanoparticles occurs due to supersaturation [32]. Pearl milling employs glass or zirconium pearls to reduce the particle size of the dispersed drug particles [33]. The major drawback of this technique is the difficulty in aseptic processing and the risk of contamination from the pearls. In case of high-pressure homogenization, the drug suspension passes from a 3-cm diameter cylinder through a 25 μm space under the tremendous pressure of 1500 bar. A very fine particle size range is obtained depending on the texture of the drug, pressure employed and number of homogenization cycles. This technique is attractive by the relative ease with which an aseptic production can be carried out [28, 34]. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone [28, 35–37]. All of the formulations are in the research stage. However, studies must be done for potential degradation of the drug, increased toxicity, and electrically induced agglomeration by particle size reduction. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form.

4.2. Modifications of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form, although the polymorphs of a compound could be a member of the same crystal system [38, 39]. Different polymorphs of a drug are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability and so on. Polymorphs of a drug exhibit differences in biological activity for obvious reasons. Therefore, bioavailability of a drug can be enhanced if appropriate studies are done to detect polymorphs with higher solubility. It is important to realize that the selection of a polymorph of a drug should strike a balance between solubility and stability to retain its potency over the shelf life period [40]. Broadly, polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantropic system, one polymorph form can change reversibly into another at a definite transition temperature below the melting point while no reversible transition is possible for monotropes. Once the drug has been characterized under one of these categories, further studies involve the detection of the metastable form of the crystal. Metastable forms are associated with higher energy and thus higher solubility [41]. Similarly, the amorphous form of a drug is always more suited than the crystalline form due to higher energy associated and increased surface area. At constant temperature and pressure, the free energy differences between polymorphs can be calculated by eq. (7).

$$\Delta G_t = RT \ln [C_s \text{ Polymorph A}/C_s \text{ Polymorph B}] \quad (7)$$

where ΔG_t is the free energy difference, C_s is the saturation solubility and T is temperature.

Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. However, as mentioned before, the possibility of the conversion of the high energy metastable polymorph to a low energy crystalline form having low solubility cannot be ruled out during manufacture and storage [9]. This approach has been exploited for drugs including carbamazepine, cortisone acetate, novobiocin, and chlorpropamide [9, 42–44].

4.3. Complexation

This approach to improve solubility employs π-Donor/π-acceptor mechanism or complexing agents like cyclodextrins and its derivatives. Nicotinamide enhances the solubility of diazepam and progesterone by the π-Donor/π-acceptor mechanism. Similarly, caffeine complexes with salts of benzoic/salicylic acid by the same mechanism resulting in increased solubility [9, 45].

4.3.1. Cyclodextrins

Cyclodextrins are toroid shaped non-reducing cyclic oligosaccharides obtained from starch by the action of cyclodextrin glycosyltransferase (CGTase) enzyme. Generally, cyclodextrins consist of 6, 7 or 8 D-glucopyranosyl units connected by alpha-(1,4) glycosidic linkages known as α-, β- and γ- cyclodextrins respectively. As shown in Fig. 1, the cyclodextrin molecule is hydrophilic on the outside due to the presence of the secondary and primary hydroxyl groups thus making it aqueous soluble. However, the inner core presents a hydrophobic environment due to the presence of electron rich glycosidic oxygen atoms enabling complex formation with poorly soluble drugs. Assuming a 1 : 1 complexation, the mechanism of drug release from cyclodextrin can be depicted by two important parameters, complexation strength or constant (K), and lifetime of the complex (τ) measured when equilibrium is disturbed. The association process of the drug with cyclodextrin can be viewed as

$$D_f + CyD_f \overset{K}{\longleftrightarrow} DcyD \quad (8)$$

where D_f represents free drug, CyD_f represents free cyclodextrin and DcyD represents the drug-cyclodextrin com-

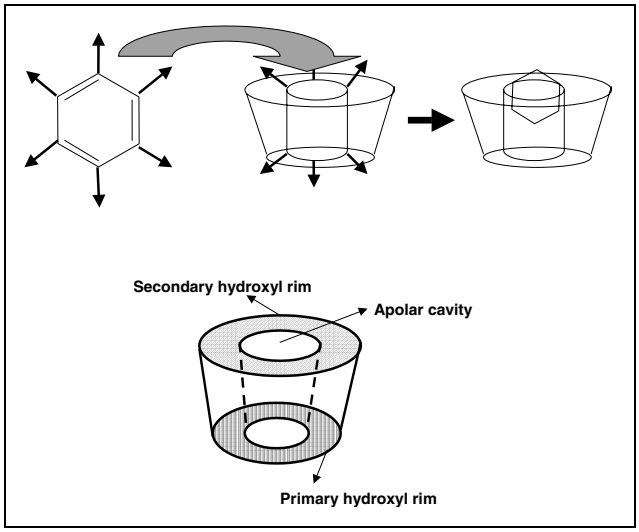


Fig. 1: Molecular shape and structure of cyclodextrin and inclusion of hydrophobic drugs in the core

plex. Considering the above representation, the two mentioned parameters could be calculated from eq. (9) and eq. (10) respectively [46].

$$K = \frac{k_f}{k_r} = \frac{[DcyD]}{([D_f]\,[CyD_f])}\,, \qquad (9)$$

$$k_{obs} = \frac{1}{\tau} = k_f\,([CyD_f] + [D_f]) + k_\tau\,, \qquad (10)$$

where k_f – forward rate constant, k_r – reverse rate constant, k_{obs} – observed rate constant for establishing the equilibrium after its perturbed, k_τ – estimates τ after complete dissociation of the complex after dilution.

The forward rate and reverse rate constants of molecules (including p-nitrophenolate, n-butanol, n-pentanol, etc) to and from cyclodextrins determined by pulse voltammetry [47] and ultrasonic relaxation studies [48, 49] were found to be in the range of 10^8–10^7 M^{-1} s^{-1} (relatively independent of K) and 10^5 s^{-1}, respectively. The lifetime of the complex was in the range of a few microseconds [50–53].

Cyclodextrins (CDs) are eliminated from the body mostly by renal filtration. Derivatives of cyclodextrin such as methyl CDs, hydroxypropyl CDs, sulfoalkylated CDs and sulfated CDs with improved aqueous solubility are gaining dominance rather than the natural CDs. Sporanox™, itraconazole/HP-β-CD and Clorocil™, chloramphenicol/methyl-β-CD are available on the market [54]. Other drugs such as fenbufen and ibuprofen have been complexed with β-CD and digoxin in γ- CD to improve dissolution rate [9, 55].

4.4. Drug dispersion in carriers

The dispersion of a poorly aqueous soluble drug in a highly soluble carrier helps increase the release rate and thus improve bioavailability. Solid dispersions like eutectic combinations (non-molecular) and solid solutions (molecular) are based on this approach [56]. Eutectic mixtures of sulphathiazole and chloramphenicol in urea were found to have higher dissolution rates [21, 57].

4.4.1. Solid solutions

Solid solutions were first developed by Levy [58] and Kanig [59]. The advantages offered by solid solutions include dispersion of the drug at a molecular level in carrier [60], absence of crystal structure of drug in solid solution [61], improved wettability and/or solubilization or cosolvent effect [21]. Moreover, a metastable polymorph of drug with higher solubility is precipitated even in the case of supersaturation during the process of dissolution [62, 63]. In preparing solid solutions, the mutual solubility of the drug and the carrier and the dose of the drug should be considered. Solid solutions can be prepared by the hot melt method or the solvent evaporation method. The prerequisite for the hot melt method is the miscibility of drug and carrier in molten form while for the solvent method, a common solvent for drug and carrier is essential. Due to the toxicity potential of the organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions. The hot melt extrusion method exposes the drug and the carrier to high temperature only for about a minute reducing the chance of degradation of drug due to prolonged exposure to elevated temperature [21]. The technique was developed by Speiser [64, 65] and Hüttenrauch [66] for pharmaceutical purposes.

The commonly used carriers for preparing solid solutions include polyethylene glycol (PEG), polyvinyl pyrrolidone) PVP, cellulose derivatives (including hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethylethylcellulose (CMC), hydroxypropyl methylcellulose phthalate (HPMCP)), polyacrylates and polymethyl acrylates, urea, sugars, polyols, emulsifiers and organic acid derivatives [21]. The solid dispersion technique was applied to drugs such as griseofulvin in PVP [67], and glyburide and oxazepam in PEG 4000 [68, 69].

4.5. Solubilization and surfactants

Another approach of increasing bioavailability of the poorly soluble drug is through solubilization of the drug by means of surfactants. The solubilization approach involves formulating microemulsions or Self-emulsifying Drug Delivery Systems (SEDDS). Vigorous stirring of two immiscible phases, oil and water, in the presence of a single surfactant, usually forms coarse emulsions. Thus, energy is used to increase the surface area of the internal phase while attempting to decrease its droplet size in the continuous phase. Coarse emulsions have an internal phase droplet diameter ranging from 50 to 0.1 μm making them cloudy in appearance. Moreover the internal phase droplets in coarse emulsion aggregate and coalesce over time tending towards the lower free energy level. This results in creaming, cracking or phase inversion causing instability of the coarse emulsions.

A microemulsion is a four-component system consisting of external phase, internal phase, surfactant and cosurfactant. The addition of cosurfactant, which is predominantly soluble in the internal phase unlike the surfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion often termed as "microemulsion" due to the magnitude of the internal phase droplet diameter (< 0.1 μm). The formation of microemulsion is spontaneous and does not involve the input of external energy as in the case of coarse emulsions. There are many controversial theories related to the formation of microemulsions. One theory considers negative interfacial tension while another considers swollen micelles. The surfactant and the cosurfactant alternate each other forming a mixed film at the interface contributing to the stability of the microemulsion as shown in Fig. 2 [70]. SEDDS are homogeneous mixtures of oils, surfactants with the poorly soluble drugs that form fine O/W emulsions upon dilution with the GI fluids. Sandimmune® and Neoral® are the commercial preparations of poorly aqueous soluble cyclosporin A employing this approach to increase bioavailability [71].

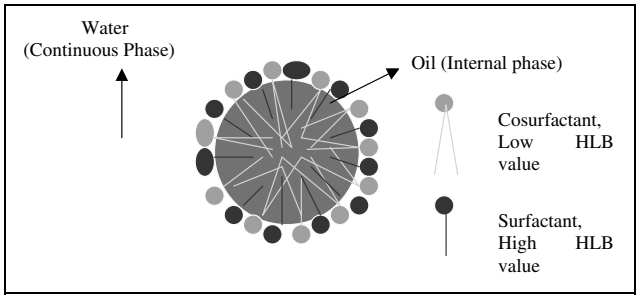


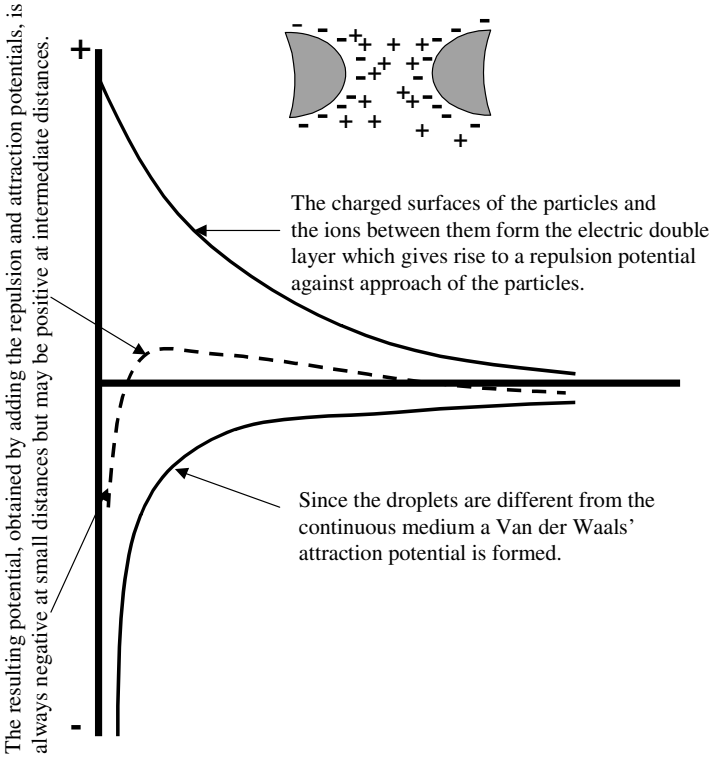
Fig. 2: Formation of microemulsion

4.5.1. Theory of emulsions

Emulsion is defined as the dispersion of two immiscible liquids, in which the internal phase is distributed uniformly in the form of globules through out the external or continuous phase. When two immiscible liquid phases are agitated to make a dispersion, the system is driven to a higher energy state. Although droplets of the two phases are formed initially, they eventually coalesce to form separate layers leading to a lower free energy state. Broadly, emulsions tend to be either O/W or W/O type. Other than the coarse macroemulsions, multiple emulsions such as W/O/W and O/W/O type can also be produced. The presence of an emulsifying agent, which interacts at the interface of the internal phase and the continuous phase, is essential for the formation of a stable emulsion. Emulsifying agents can either be synthetic surfactants or naturally occurring emulsifiers such as gums or finely divided clays. Synthetic emulsifying agents are most commonly employed for the production of emulsions. The emulsifying agents possess both hydrophilic and lipophilic properties measured by the arbitrary scale of HLB (Hydrophilic Lipophilic Balance). Emulsifying agents with HLB of 8 to 16 have predominantly hydrophilic properties forming O/W type of emulsion while those with HLB values of 3 to 8 tend to be more lipophilic forming W/O type of emulsions. Synthetic emulsifiers can be categorized as anionic, cationic, nonionic and amphoteric depending on their ionic behavior. Nonionic surfactants are predominantly used due to their highest compatibility with other components and low toxicity. They stabilize the emulsion system by decreasing the interfacial free energy of the dispersion system. Moreover, they form a barrier at the interface preventing coalescence of the dispersed phase. The barrier formation is made possible by the close packing of the surfactant molecules at the interface into a rigid film [72, 73]. In certain cases, emulsifiers also stabilize the emulsion by inducing repulsive electrical forces between the droplets of the internal phase. The potential of the double layer of the droplet resulting in repulsive forces can be explained by the DLVO theory. The double layer formation occurs in the presence of electrolytes in the continuous phase that act as counterions to the charged portion of the emulsifier at the interface. The DLVO theory relates the stability of the emulsions to two potentials, the negative Van der Waals potential and the positive double layer potential as shown in Fig. 3. For o/w emulsions containing low electrolyte concentrations, a zeta potential of 30 mV or higher confers stability to the system. However, for W/O emulsions containing high electrolyte concentrations or for w/o emulsions, there is no significant effect of zeta potential on the emulsion stability [73].

4.5.2. Micelles

The adsorption of the surfactant molecules at the interface reaches an upper limit at a certain concentration of the emulsifier and the excess surfactant begins to concentrate in the continuous phase forming molecular aggregates, also referred to as micelles. The concentration of the surfactant at which this phenomenon occurs is known as the critical micelle concentration (CMC), as shown in Fig. 4. The CMC is in the range of 0.05–0.10% for most of the surfactants. The association of the amphiphilic surfactant molecules above CMC occurs due to the disruption of the hydrogen bonds in water in the case of O/W emulsions. The free energy of attraction pertaining to hydrogen bonds in water is more than three times greater than the free energy of attraction between the hydrocarbon portion of



The two potentials involved in the DVLO theory are from overlap of the electric double layer (top line) and from the Van der Waals interaction (lower line). A sufficient positive value of the total potential (dashed line) gives colloidal stability.

Fig. 3:
Potentials involved in DLVO [91, 92]

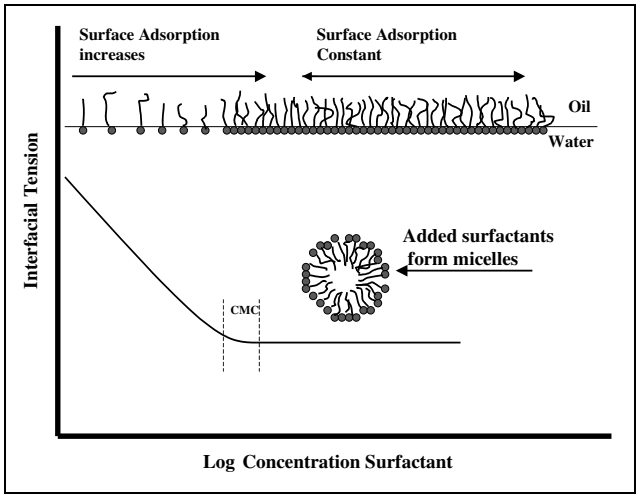


Fig. 4: Schematic diagram showing surfactant adsorption [93]

the surfactant and water. In the case of W/O emulsions, the association occurs as a result of the dipole-dipole interactions of the polar head groups and the dispersion forces between the non-polar tails and the continuous phase.

4.5.3. Microemulsions

In 1981, Dannielson and Lindman defined a microemulsion as 'a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution' [74, 75]. Fig. 5 shows the most common microemulsion microstructures. As mentioned earlier, microemulsion formation does not require input of energy thus reducing the cost of production drastically. Several theories have been proposed for the formation of microemulsion including: (i) solubilization theories, (ii) swollen micelles, (iii) mixed film theory, and (iv) thermodynamic treatment. Solubilization theory considers microemulsions as solutions with solubilized water or solubilized hydrocarbons. This approach is based on the ternary phase equilibria diagrams, which indicate that microemulsions are monophasic, fluid, isotropic systems. Two-phase thermodynamically unstable emulsions could exist outside the limit of micellar range [76]. Microemulsions are potential drug delivery systems for poorly aqueous soluble drugs due to their ability to solubilize the drug in the oil phase, thus increasing their dissolution rate. Even if the microemulsions are diluted after oral administration below CMC, the drug precipitated has a very fine particle size range allowing enhanced absorption [73].

Aqueous swollen micelles were proposed by Adamson, who utilized the concept of balance between Laplace and osmotic pressure in W/O microemulsions [76]. Shinoda and Friberg suggested that oil is solubilized into the interior of a micelle, in the micellar aqueous solution at an appropriate temperature, resulting in a swollen micelle [73]. The mixed film theory is based on the concept that the surfactant-cosurfactant blend forms a mixed film at the oil-water interface [77]. The cosurfactant, most often a short chain alcohol alternates with the surfactant in a monomolecular layer and plays a role in increasing the fluidity and disorder of the interfacial film [78]. Spontaneous formation of microemulsion occurs with the addition of cosurfactant due to the increase in the interfacial pressure resulting in negative interfacial tension [77]. The thermodynamic consideration of the formation of microemulsion is based on the following equation (11):

$$\Delta G_f = \gamma \Delta A - T \Delta S \qquad (11)$$

where ΔG_f is the free energy of formation, γ is the surface tension of the oil-water interface, ΔA is the change in interfacial area on microemulsification, ΔS is the change in entropy of the system and T is the temperature. The high concentration of emulsifier results in significant decrease of the surface tension. Also, a favorable entropy change occurs due to the dispersion entropy from mixing of the two phases and dynamic processes including surfactant diffusion into the interface and monomer-micellar exchange. Finally, the negative free energy of formation makes spontaneous emulsification possible by tremendous increase in surface area of the internal phase [75]. Cholesteryl ester prodrugs of ibuprofen and flufenamic acid have been incorporated into phospholipid microemulsions [79].

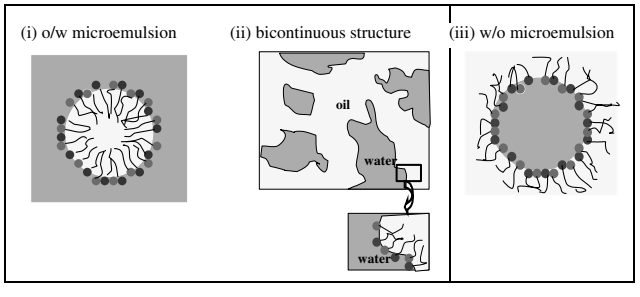


Fig. 5: Structure of microemulsion

4.5.4. Self-microemulsifying drug delivery systems (SMEDDS®)

Self-emulsifying drug delivery systems (SEDDS) are homogeneous mixtures of oils, surfactants, or alternatively, one or more hydrophilic solvents and co-solvents, which form fine O/W emulsions or microemulsions (SMEDDS®) upon dilution with the aqueous phase [80]. SMEDDS® are different from O/W microemulsions by the fact that external aqueous phase is absent and microemulsion formation occurs upon dilution with the GI fluids once orally administered. Sandimmune® (SEDDS) and Neoral® (SMEDDS®) are two successful products under this category that are currently available on the market. Both of them are formulations for the poorly aqueous soluble immunosuppressant cyclosporin A. Neoral® has demonstrated better capacity in increasing the drug uptake compared to Sandimmune® [81–83]. Sandimmune® employs olive oil, polyglycolized glycerides and hydrophilic solvent, ethanol while Neoral® employs hydrolyzed corn oil, polyglycolized glycerides, POE-castor oil derivative and hydrophilic solvent, ethanol or glycerol in the formulation [80]. Due to the presence of blend of the medium chain length triglyceride oil and surfactants based on medium chain partial glycerides, Neoral® presents less variability and better drug uptake compared to Sandimmune®. Unlike Sandimmune®, Neoral® eliminates the potential of inter- and intra-individual variation in lipolysis products of triglycerides which act as emulsifiers in the GI tract [84, 75]. Also, Sandimmune® produces a coarse emulsion, which is not reduced to colloidal dimensions in the GI tract unlike Neoral® (microemulsifying system) resulting in comparatively lower bioavailability of cyclosporin from the formulation [71].

In a study by Kim et al. [85], a microemulsion system for cyclosporin A was prepared using caprylic/capric triglyceride (Captex 355®) as the oil phase, polyoxyethylated cas-

Table 3: Analysis of non-compartmental pharmacokinetic parameters after oral administration of cyclosporin A to rats [78]

Parameters	Intravenous (1 mg/kg)	Oral (7 mg/kg)		
		Sandimmun®	Sandimmun® Neoral	Microemulsion
C_{max} (μg/ml)		1.285 ± 0.088	2.589 ± 0.322	3.275 ± 0.367
T_{max} ((h)		2.333 ± 0.441	3.000 ± 0.354	3.667 ± 0.333
AUC (μg/h per ml)	11.390 ± 0.193	12.531 ± 0.088	33.171 ± 5.534	41.322 ± 4.532
Absolute bioavailability (F)		0.157	0.416	0.518

$P < 0.05$ by the student t-test when compared with Sandimmun®
$F = [(AUC_{oral})/(dose_{oral})] \div [(AUC_{IV})/(dose_{IV})]$

tor oil (Cremophor EL®) as surfactant, diethylene glycol monoethylether (Transcutol®) as cosurfactant, and saline. Comparative studies were done with Sandimmune®, Neoral® and the experimental microemulsion system (Cremophor® EL: Transcutol®: Captex® 355, 10 : 5:4). As shown in Table 3 and Fig. 6, the maximal blood concentration (C_{max}) of cyclosporin A, and area under the curve of drug concentration vs. time profile (AUC) after oral administration of the cyclosporin A loaded experimental microemulsion was found to increase by 3.5 and 3.3 folds compared to Sandimmune®. Although no significant difference in C_{max} and AUC between this microemulsion and Neoral® was found, the absolute bioavailability from this microemulsion was increased about 3.3 and 1.25 fold compared with Sandimmune® and Neoral®, respectively. The authors (Kim et al) suggest the reduced internal droplet diameter (22 nm) of the experimental microemulsion system as a possible reason for the enhanced absolute bioavailability of cyclosporin A compared to Sandimmune® (internal droplet diameter upon dilution, 864 nm) and Neoral® (internal droplet diameter upon dilution, 39 nm).

Another category of solubilization approach includes submicron emulsion for poorly soluble drugs. Although submicron emulsions do not fit the definition of microemulsions, they have a fine internal phase droplet diameter and low concentrations of emulsifier (surfactant and cosurfactant) that are potentially toxic *in vitro*. The fine globule size of the sub-micron emulsion presents a potential to enhance the absorption of poorly soluble drugs and also have a greater physical stability compared to coarse emulsions. However, unlike microemulsions, the preparation of sub-micron emulsions requires input of energy. These delivery systems are generally produced by techniques of hyperhomogenization and microfluidization. The emulsification forces in these processes include high shear (laminar flow), turbulence (inertial force) and cavitation (vapor bubble implosion). The process parameters can be set to obtain optimum droplet diameter of the internal phase [86].

The advantages offered by the lipid based drug delivery systems such as microemulsions and SMEDDS include: improved drug solubilization and protection against enzymatic hydrolysis, potential for enhanced absorption afforded by surfactant-induced membrane and thus permeability changes, and accumulation in the regional lymph nodes [87, 88] and retention therein in high concentration over an extended period, providing sustained drug delivery [89]. As mentioned by Charman et al. [90], the components of the mixed micellar phase influence the intestinal permeability of poorly aqueous soluble drugs mainly by three mechanisms, including: (i) lipid digestion products and bile salts enhancing absorption by increasing the paracellular and transcellular permeation, (ii) solubilization of lipophilic drugs within bile salt mixed micelle may facilitate diffusion through aqueous layers increasing absorption, and (iii) decrease in intermicellar 'free' fraction of the drug by solubilization increasing the potential for absorption.

5. Conclusion

Solubility and permeability are the two important parameters affecting bioavailability of drug substances. An understanding of the Biopharmaceutic Classification System allows one to tackle bioavailability problems associated with orally administered drugs. The "rule of 5" pneumonic developed by Pfizer Central Research Division gives a good estimate of permeability of a drug candidate. The aqueous solubility of the Class II drugs can be improved by either chemical or formulation approaches. Formulation approaches are preferred in most of the situations due to

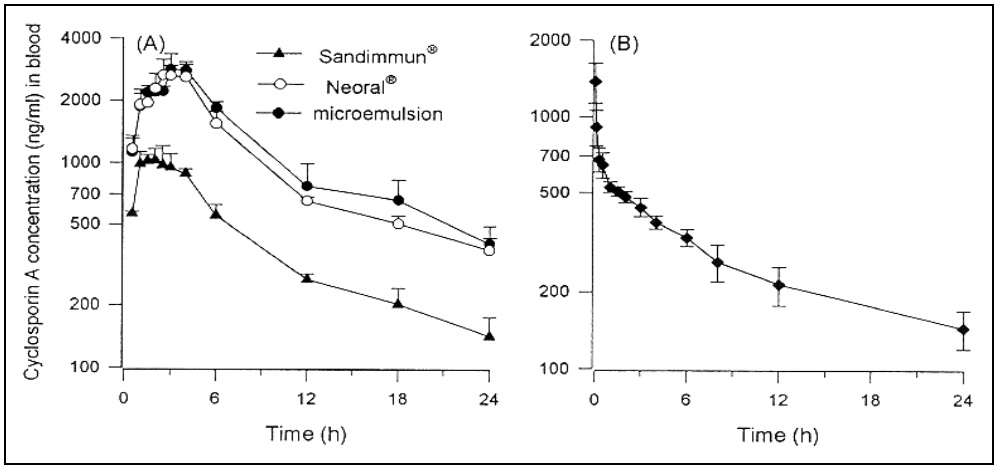


Fig. 6:
Plasma concentration of cyclosporin A after oral and intravenous administration of Sandimmune® and Neoral®, (A) plasma concentration time profile of cyclosporin A after oral administration of Sandimmune®, Sandimmun Neoral® and microemulsion, (B) plasma concentration time profile after intravenous administration of cyclosporin A [85]

the ease of application and reduced time and cost in development. Various formulation approaches including cosolvency, particle size reduction, modification of the crystal habit, complexation, solubilization, drug dispersion in carriers are currently being employed. The selection of a particular approach in preference to others depends on the extent of bioavailability and commercial success. Lipid based drug delivery systems based on solubilization approach are under current investigation. Although not many drug formulations employing this approach are available commercially, the approval of Neoral® within a short span of time has attracted interest of many researchers in these lipid based drug delivery systems for poorly soluble drugs.

References

1 Lipper, R. A.: Modern Drug Discovery **2**, 55 (1999)
2 Panchagnula, R.; Thomas, N. S.: Int. J. Pharm. **201**, 131 (2000)
3 Shargel, L.; Yu, A.: Applied Biopharmaceutics and Pharmacokinetics, 4 Ed., p. 146, Appleton & Lange, Stamford, Connecticut 1999
4 Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R.: Pharm. Res. **12**, 413 (1995)
5 Lobenberg, R.; Amidon, G. L.: Eur. J. Pharm. Biopharm. **50**, 3 (2000)
6 Jounela, A. J.; Pentikainen, P. J.; Sothmann, A.: Eur. J. Clin. Pharmacol. **8**, 365 (1975)
7 Dressman, J. B.; Fleisher. D.: J. Pharm. Sci. **75**, 109 (1986)
8 Shah, V. P.; Konecny, J. J.; Everett, R. L.; McCullough, B.; Noorizadeh, A. C.; Skelly, J. P.: Pharm Res. **6**, 612 (1989)
9 Horter, D.; Dressman, J. B.: Adv. Drug. Del. Rev. **25**, 3 (1997)
10 Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P.: Pharm. Res. **15**, 11 (1998)
11 Nerst, W.; Brunner, E.: Z. Physik. Chem. **47**, 52 (1904)
12 Levich, V. G.: Physicochemical Hydrodynamics, Englewood Cliffs, Prentice Hall, New Jersey 1962
13 Noyes, A. S.; Whitney, W. R.: J. Am. Chem. Soc. **19**, 930 (1897)
14 Yalkowsky, S. H.: Solubility and solubilization of nonelectrolytes; in: Yalkowsky, S.H (Ed.): Techniques of solubilization of drugs, pp. 1–14, Marcel Dekker, New York 1981
15 Amidon, G. L.: Drug derivatization as a means of solubilization: physical and biochemical strategies; In: Yalkowsky, S. H., (Ed.): Techniques of solubilization of drugs. pp. 183–211 Marcel Dekker, New York 1981
16 Stella, V. J.; Martodihardjo, S.; Terada, K.; Rao, V. M.: J. Pharm. Sci. **87**, 1235 (1998)
17 Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R.: J. Med. Chem. **37**, 3443 (1994)
18 Kemp, D. J.; March, K. C.; Denissen, L. F.; McDonald, E.; Vasavanonda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Long, X. P.; Wideburg, N. E.; Salidivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard,J. M.; Norbeck, D. W.: Proc. Natl. Acad. Sci. USA **92**, 2484 (1995)
19 Berge, S. M.; Bighley, L. D.; Monkhouse, D. C.: J. Pharm. Sci. **66**, 1, (1977)
20 Ansel, H. C.; Popovich, N. G.; Allen, L. V. Jr.: Pharmaceutical Dosage forms and Drug Delivery Systems, 6 Ed., p 109, Williams & Wilkins 1995
21 Leuner, C.; Dressman, J. B.: Eur. J. Pharm. Biopharm. **50**, 47 (2000)
22 Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J.: Adv. Drug. Del. Rev. **46**, 3 (2001)
23 Aungst, B. J.: J. Pharm. Sci. **82**, 979 (1993)
24 Müller R. H.; Peters, K.; Becker, R.; Kruss, B.: Proceed. Intern. Symp. Control. Rel. Bioact. Mater. **22**, 574 (1995)
25 Chaumeil, J. C.: Methods Find. Exp. Clin. Pharmacol. **20**, 211 (1998)
26 McInnes, G. T.; Asbury, M. J.; Ramsay, L. E.; Shelton, J. R.; Harrison, I. R.: J. Clin. Pharmacol. **22**, 410 (1982)
27 Rawlins, E. A.: Bentley's Textbook of Pharmaceutics, 8 Ed., p. 6, Bailliere Tindall, London, 1977
28 Müller, R. H.; Jacobs, C.; Kayser, O.: Adv. Drug. Del. Rev. **47**, 3 (2001)
29 Duchene, D.; Ponchel, G.: Eur. J. Pharm. Biopharm. **44**, 15 (1997)
30 Nyström, C.; Saers, S.: Solid dispersions for fast release and dissolution of drug with low aqueous solubility in: Formulation of poorly – available drugs for oral administration, European Symposium Paris, 5–6 February, p. 94, APGI Swedish Academy of Pharmaceutical Sciences 1996
31 Nyström, C.: Dissolution properties of soluble drugs: Theoretical background and possibilities to improve the dissolution behaviour; in: Müller, R. H.; Benita, S.; Böhm, B.; (Eds.): Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs, p. 143 Medpharm Scientific Publishers Stuttgart 1998
32 Gaβmann, P.; List, M.; Schweitzer, A.; Sucker, H.: Eur. J. Pharm. Biopharm. **40**, 64 (1994)
33 Liversidge, G. G.; Cundy, K. C.; Bishop, J.; Czekai, D.: Surface modified drug nanoparticles, US Patent No. 5145684 (1991)
34 Müller, R. H.; Becker, R.; Kruss, B.; Peters, K.: Pharmaceutical nanosuspensions for medical administration as system of increased saturation solubility and rate of solution, US Patent No. 5858410 (1998)
35 Jacobs, C.; Kayser, O.; Müller, R. H.: Int. J. Pharm. **196**, 161 (2000)
36 Keyser, O: Int. J. Pharm. **214**, 83 (2001)
37 Jacobs, C.; Kayser, O.; Müller, R. H.: Int. J. Pharm. **214**, 3 (2001)
38 Ravin, L. T.: Preformulation; in: Swarbrick, J.; Boyland, J. C. (Eds): Encyclopedia of Pharmaceutical Technology, Vol. 12, p. 305, Marcel Dekker, New York 1995
39 Ruiz, M. A.: Int. J. Pharm. **177**, 221 (1999)
40 Agatonovic-Kustrin, S.; Wu, V.; Rades, T.; Saville, D.; Tucker, I. G.: Int. J. Pharm. **184**, 107 (1999)
41 Vippagunta, S. R.; Brittain, H. G.; Grant, D. J. W.: Adv. Drug. Del. Rev. **48**, 3 (2001)
42 Ansel, H. C.; Popovich, N. G.; Allen, L. V. Jr.: Pharmaceutical dosage forms and drug delivery systems, 6 Ed., p. 66 Williams & Wilkins 1995
43 Al-Saieq, S. S.; Riley, G. S.: Pharm. Acta Helv. **57**, 8, 1982
44 Haleblian, J.; McCrone, W.: J. Pharm. Sci. **58,** 911 (1969)
45 Rasool, A. A.; Hussain, A. A.: Dittert, L. W.: J. Pharm. Sci. **80**, 387 (1991)
46 Stella, V. J.: Adv. Drug. Del. Rev. **36**, 3 (1999)
47 Nuwer, M. J.; Odea, J. J.: Osteryoung, J. G.: J. Phys. Chem. **95**, 10070 (1991)
48 Hall, D.; Bloor, D.; Tawarah, K.; Wyn-Jones, W.: J. Chem. Soc. Faraday Trans. I **82**, 2111 (1986)
49 Rohrbach, R. P.; Rodriguez, L. J.; Eyring, E. M.; Wojcik, J. F.: J. Phys. Chem. **81,** 944 (1977)
50 Clarke, R. J.; Coates, J. H.; Lincoln, S. F.: Carb. Res. **127**, 181 (1983)
51 Clarke, R. J.; Coates, J. H.; Lincoln, S. F.: J. Chem. Soc. Faraday Trans. I **80**, 3119 (1984)
52 Schiller, R. L.; Lincoln, S. F.; Coates, J. H.: J. Chem. Soc. Faraday Trans. I **82**, 2123 (1986)
53 Orstan, A.: Carb. Res. **176**, 149 (1988)
54 Szente, L.; Szejtli, J.: Adv. Drug. Del. Rev. **36**, 17 (1999)
55 Miyayi, T.; Inoue, Y.; Acarturk, F.; Imai, T.; Otagiri, M.; Uekama, K.: Acta Pharm. Nord. **4**, 17 (1992)
56 Chiou, W. L.; Riegelman, S.: J. Pharm. Sci. **60**, 1281 (1971)
57 Sekiguchi, K.; Obi, N.; Ueda, Y.: Chem. Pharm. Bull. **12**, 134 (1964)
58 Levy, G.: Am. J. Pharm. **135**, 78 (1963)
59 Kanig, J. L.: J. Pharm. Sci. **53**, 188 (1964)
60 Goldberg, A. H.; Gibaldi, M.; Kanig, J. L.; Mayersohn, M.: J. Pharm. Sci. **55**, 581 (1966)
61 Taylor, L. S.; Zografi, G.: Pharm. Res. **14**, 1691 (1997)
62 Hilton, J. E.; Summers, M. P.: Int. J. Pharm. **31**, 157 (1986)
63 Ford, J. L.; Rubinstein, M. H.: Pharm. Acta Helv. **53**, 327 (1978)
64 Speiser, P.: Pharm. Acta. Helv. **41**, 321 (1966)
65 Adel El-Egakey, M.; Soliva, M.; Speiser, P.: Pharm. Acta. Helv. **46**, 31 (1971)
66 Hüttenrauch, R.: Pharmazie **29**, 297 (1974)
67 Mayerson, M.; Gibaldi, M.: J. Pharm. Sci. **55**, 1323 (1966)
68 Betageri, G. V.; Makarla, K. R.: Int. J. Pharm. **126**, 155 (1995)
69 Gines, J. M.; Arias, M. J.; Moyano, J. R.; Sanchezsoto, P. J.: Int. J. Pharm. **143**, 247 (1996)
70 Gullapalli, R. P.; Sheth, B. B.: Eur. J. Pharm. Biopharm. **48**, 233 (1999)
71 Pouton, C. W.; Eur. J. Pharm. Sci., Suppl. 2, S93 (2000)
72 Schulman, J. J.; Cockbain, E. G.: Trans. Faraday Soc. **36**, 651 (1940)
73 Lieberman, H. A.; Rieger, M. M.; Banker, G. S.: Pharmaceutical Dosage Forms, Disperse Systems, Volume 1, Marcel Dekker, Inc, New York and Basel 1988
74 Danielsson, I.; Lindman, B.: Colloids and Surfaces **3**, 391 (1981)
75 Lawrence, M. J.; Rees, G. D.: Adv. Drug. Del. Rev. **45**, 89 (2000)
76 Prince, L. M.: Microemulsions, Theory and Practice, p. 18, Academic Press, Inc. 1977
77 Garti, N.; Aserin, A.; in: Benita, S.: Microencapsulation, p. 411, Marcel Dekker, New York 1996
78 Leung, R.; Shah, D. O.; In: Rossof, M. (Ed.): Controlled Release of Drugs: Polymers and Aggregate Systems, p. 85, VCH, New York 1989
79 Murtha, J. L.; Ando, H. Y.: J. Pharm. Sci. **83**, 1222 (1994)
80 Gershanik, T.; Benita, S.: Eur. J. Pharm. Biopharm. **50**, 179 (2000)
81 Holt, D. W.; Muller, E. A.; Kovarik, J. M.; van Bree, J. B.; Kutz K.: Transplant. Proc. **26**, 2935 (1994)
82 Kovarik, J. M.; Mueller, E. A.; van Bree, J. B.; Tetzloff, W.; Kutz, K.: J. Pharm. Sci. **83**, 444 (1994)
83 Mueller, E. A.; Kovarik, J. M.; van Bree, J. B.; Tetzloff, W.; Grevel, J.; Kutz, K.: Pharm. Res. **11**, 301 (1994)
84 Hutchison, K.: Digestible emulsions and microemulsions for optimum oral delivery of hydrophobic drugs, Bulletin Technique Gattefosse,

Gattefosse SA, France, **87**, 67 (1994)
85 Gao, Z. G.; Choi, H. G.; Shin, H. J.; Park, K. M.; Lim, S. J.; Hwang, K. J.; Kim, C. K. A.: Int. J. Pharm. **161**, 75 (1988)
86 Silvestri, S.; Ganguly, N.; Tabibi, E.: Pharm. Res. **9**, 1347 (1992)
87 Takahashi, T.; Ueda, S.; Kono, K.; Majima, S.: Cancer **38**, 1507 (1976)
88 Swenson, E. C.; Curatolo, W. J.: Adv. Drug. Deli. Rev. **8**, 39 (1992)
89 Takahashi, T.; Mizuno, M.; Fujita, Y.; Ueda, S.; Nishioka, B.: Gann **64**, 345 (1973)
90 Humberstone, A. J.; Charman, W. N.: Adv. Drug. Del. Rev. **25**, 103 (1997)
91 Derjaguin, B.; Landau, L. D.: Acta Physiochem. USSR 14, 633 (1941)
92 Verwey, E. J. U.; Overbeek, J. T. G.: Theory and Stability of Lyophobic Colloids, Elsevier, Amsterdam 1948
93 Friberg, S. E.; El-Nohaly: in: Rieger, M. H. (ed.): Surfactants in Cosmetics, Marcel Dekker, New York 1985

Received June 7, 2001
Accepted November 20, 2001

Sudip K. Das, M.Pharm., Ph. D.
Associate Professor of Pharmaceutics
Idaho State University
Department of Pharmaceutical Sciences
College of Pharmacy
970 South 5th Avenue
Campus Box 8334
Pocatello, ID 83209-8334
das@pharmacy.isu.edu